

WHAT IS CLAIMED IS:

- Sub b2*
- 1 1. Use of a humanized antibody to alpha-4 integrin in
2 the manufacture of a medicament for treating a disease
3 selected from the group consisting of asthma, atherosclerosis,
4 AIDS dementia, diabetes, inflammatory bowel disease,
5 rheumatoid arthritis, transplant rejection, graft versus host
6 disease, tumor metastasis, nephritis, atopic dermatitis,
7 psoriasis, myocardial ischemia, and acute leukocyte mediated
8 lung injury.
 - 1 2. The use according to claim 1, wherein the disease is
2 asthma.
 - 1 3. The use according to claim 1, wherein the disease is
2 atherosclerosis.
 - 1 4. The use according to claim 1, wherein the disease is
2 AIDS dementia.
 - 1 5. The use according to claim 1, wherein the disease is
2 diabetes.
 - 1 6. The use according to claim 1, wherein the disease is
2 inflammatory bowel disease.
 - 1 7. The use according to claim 1, wherein the disease is
2 rheumatoid arthritis.
 - 1 8. The use according to claim 1, wherein the disease is
2 transplant rejection.
 - 1 9. The use according to claim 1, wherein the disease is
2 graft versus host disease.
 - 1 10. The use according to claim 1, wherein the disease is
2 tumor metastasis.

1 11. The use according to claim 1, wherein the disease is
2 nephritis.

1 12. The use according to claim 1, wherein the disease is
2 atopic dermatitis.

1 13. The use according to claim 1, wherein the disease is
2 psoriasis.

1 14. The use according to claim 1, wherein the disease is
2 myocardial ischemia.

1 15. The use according to claim 1, wherein the disease is
2 acute leukocyte-mediated lung injury.

1 16. The use according to claim 17, wherein the disease
2 is adult respiratory distress syndrome.

a) 1 17. The use according to ~~any one of the preceding claims~~
2 wherein the humanized antibody is a humanized form of the
3 mouse 21.6 antibody.

1 18. The use according to claim 17, wherein the humanized
2 antibody comprises a humanized heavy chain and a humanized
3 light chain:

4 (1) the humanized light chain comprising three
5 complementarity determining regions (CDR1, CDR2 and CDR3)
6 having amino acid sequences from the corresponding
7 complementarity determining regions of the mouse 21-6
8 immunoglobulin light chain variable domain designated SEQ. ID.
9 No. 2, and a variable region framework from a human kappa
10 light chain variable region framework sequence except in at
11 least one position selected from a first group consisting of
12 L45, L49, L58 and L69, wherein the amino acid position is
13 occupied by the same amino acid present in the equivalent
14 position of the mouse 21-6 immunoglobulin light chain variable
15 region framework; and

16 (2) the humanized heavy chain comprising three
17 complementarity determining regions (CDR1, CDR2 and CDR3)
18 having amino acid sequences from the corresponding
19 complementarity determining regions of the mouse 21-6
20 immunoglobulin heavy chain variable domain designated SEQ. ID.
21 No. 4, and a variable region framework from a human heavy
22 chain variable region framework sequence except in at least
23 one position selected from a second group consisting of H27,
24 H28, H29, H30, H44, H71, wherein the amino acid position is
25 occupied by the same amino acid present in the equivalent
26 position of the mouse 21-6 immunoglobulin heavy chain variable
27 region framework;

28 wherein the humanized immunoglobulin specifically binds
29 to alpha-4 integrin with a binding affinity having a lower
30 limit of about 10^7 M^{-1} and an upper limit of about five-times
31 the binding affinity of the mouse 21-6 immunoglobulin.

1 19. The use according to claim 18, wherein the humanized
2 light chain variable region framework is from an RE1 variable
3 region framework sequence except in at least one position
4 selected from the first group, and except in at least one
5 position selected from a third group consisting of positions
6 L104, L105 and L107, wherein the amino acid position is
7 occupied by the same amino acid present in the equivalent
8 position of a kappa light chain from a human immunoglobulin
9 other than RE1.

1 20. The use according to claim 19, wherein the humanized
2 heavy chain variable region framework is from a 21/28'CL
3 variable region framework sequence.

1 21. The use according to claim 20, wherein the humanized
2 light chain variable region framework comprises at least three
3 amino acids from the mouse 21.6 immunoglobulin at positions in
4 the first group and three amino acids from the kappa light
5 chain from the human immunoglobulin other than RE1 at
6 positions in the third group, and the humanized heavy chain
7 variable region framework comprises at least five amino acids

8 from the mouse 21.6 immunoglobulin at positions in the second
9 group.

1 22. The use according to claim 21, wherein the humanized
2 light chain variable region framework is identical to the RE1
3 light chain variable region framework sequence except for the
4 at least three positions from the first group and the three
5 positions from the third group, and the heavy chain variable
6 region framework is identical to the 21/28'CL heavy chain
7 variable region framework sequence except for the at least
8 five positions from the second group.

1 23. The use according to claim 22, wherein the at least
2 three positions from the first group are positions L45, L58
3 and L69, and at the least five positions from the second group
4 are positions H27, H28, H29, H30 and H71.

1 24. The use according to claim 23, wherein the humanized
2 light chain comprises complementarity determining regions that
3 are identical to the corresponding complementarity determining
4 regions of the mouse 21-6 heavy chain, and the humanized heavy
5 chain comprises complementarity determining regions that are
6 identical to the corresponding complementarity determining
7 regions of the mouse 21-6 heavy chain, except that the CDR3
8 region of the humanized heavy chain may or may not comprise a
9 phenylalanine residue at position H98.

1 25. The use according to claim 24, wherein the amino
2 acid sequence of the mature light chain variable region is the
3 sequence designated La (SEQ. ID NO:7) in Fig. 6 and the amino
4 acid sequence of the mature heavy chain variable region is Ha
5 (SEQ. ID NO:11) in Fig 7.

1 26. The use according to claim 25, wherein the humanized
2 antibody is a Fab fragment.

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